

Embracing different approaches to estimating HIV incidence, prevalence and mortality

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on Estimates, Modelling and Projections

Background: Joint United Nations Programme on HIV/AIDS (UNAIDS) and Murray *et al.* have both produced sets of estimates for worldwide HIV incidence, prevalence and mortality. Understanding differences in these estimates can strengthen the interpretation of each.

Methods: We describe differences in the two sets of estimates. Where possible, we have drawn on additional published data to which estimates can be compared.

Findings: UNAIDS estimates that there were 6 million more people living with HIV (PLHIV) in 2013 (35 million) compared with the Murray *et al.* estimates (29 million). Murray *et al.* estimate that new infections and AIDS deaths have declined more gradually than does UNAIDS. Just under one third of the difference in PLHIV is in Africa, where Murray *et al.* have relied more on estimates of adult mortality trends than on data on survival times. Another third of the difference is in North America, Europe, Central Asia and Australasia. Here Murray *et al.* estimates of new infections are substantially lower than the number of new HIV/AIDS diagnoses reported by countries, whereas published UNAIDS estimate tend to be greater. The remaining differences are in Latin America and Asia where the data upon which the UNAIDS methods currently rely are more sparse, whereas the mortality data leveraged by Murray *et al.* may be stronger. In this region, however, anomalies appear to exist between the both sets of estimates and other data.

Interpretation: Both estimates indicate that approximately 30 million PLHIV and that antiretroviral therapy has driven large reductions in mortality. Both estimates are useful but show instructive discrepancies with additional data sources. We find little evidence to suggest that either set of estimates can be considered systematically more accurate. Further work should seek to build estimates on as wide a base of data as possible.

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Introduction

Murray *et al.* [1] have recently published estimates of the number of new HIV infections, the number of persons

living with HIV (PLHIV) and the number of AIDS deaths for all countries. These can be contrasted with other estimates released by Joint United Nations Programme on HIV/AIDS (UNAIDS) [2]. These two sets of estimates

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are computed in related but different ways and it should, therefore, come as no surprise that, despite broad similarities, there are some differences in the estimates. However, whereas Murray *et al.* suggest that their approach can unequivocally be preferred, we believe that it is important to understand the differences that exist between the two sets of estimates in order to know how to interpret their respective findings. Given the importance attached to estimates in global health, we also reflect upon alternative ways in which country estimates can be generated.

Different approaches

The differences between the Murray *et al.* and the UNAIDS approaches can be summarised by the data upon which the estimates are based. UNAIDS derives estimates using data on HIV prevalence in most settings with generalised epidemics and some settings with concentrated epidemics (Box 1). A model is fit to these data in order to generate estimates of incidence, deaths and other quantities. In some settings (mostly high-income countries), estimates are configured to align with case-report surveillance in others. Estimates are computed by countries, with technical assistance from UNAIDS, and results are tested for their consistency with local surveillance and program data.

In contrast, Murray *et al.* base most of their estimates on UNAIDS outputs that are then combined with their own estimates of all-cause and cause-specific death rates. Candidate epidemiological trajectories for a particular country are generated, based on previously generated results by UNAIDS but with Murray *et al.* applying their own assumptions for, among other factors, HIV survival rates and the distribution of incidence by age and sex. Final estimates are generated by selecting from among the candidate trajectories those that imply a better agreement with their estimates of deaths. Estimates of mortality rates are based on data from vital registration systems where possible, and from other available data and model-based extrapolations elsewhere. In lower-level epidemic settings wherein AIDS cause-specific mortality is used, there is some reclassification of deaths that is intended to account for the misassignment of AIDS-related deaths to another cause.

Thus, the UNAIDS and the Murray *et al.* estimates are not independent, with the latter estimates relying on the same epidemiologic models used by UNAIDS but with the additional influence of their own estimates of mortality.

Different results

These different approaches give reasonably similar results, as has been highlighted previously [3]. However, there are

interesting differences: Murray *et al.* estimate that there are fewer PLHIV than UNAIDS has reported, and Murray *et al.* estimates suggest that recent reductions in AIDS deaths have been more modest than UNAIDS has reported. We consider each of these in turn.

Differences in the magnitude of the HIV epidemic

For 2013, the number of PLHIV is 35 million in the UNAIDS estimates and 29 million in Institute for Health Metrics and Evaluation estimates. The 6 million person difference is 17% of the UNAIDS total.

However, in the regions with the largest epidemics (Southern, Eastern, Central and West Africa), where the greatest attention of donors is focussed, the difference is small; UNAIDS estimates 25 million PLHIV, whereas Murray *et al.* estimate 23 million. This accounts for just less than one third of the difference in the overall totals of PLHIV globally.

In these areas with the largest epidemics, however, there are important differences in the historic trajectory of new infection and deaths, despite an overall agreement in PLHIV. Numbers of deaths are smaller in the Murray *et al.* estimates. This is likely because of different assumptions made about natural HIV survival [i.e. without anti-retroviral therapy (ART)]. UNAIDS bases its assumptions on direct empirical measurements from long-running population-based cohort studies [4] [11.1 years (8.7–14.2 years) for Eastern African cohorts and 11.6 years (9.8–13.7 years) for Southern Africa] for 25–29-year olds, which are also consistent with historical cohort studies in Europe, North America and Australia [5] (10.9 years (10.6–11.3 years) for 25–34-year olds)]. These same survival times are applied across epidemic settings. Murray *et al.* allow median survival to vary between 3.6 and 29.5 years, based on a new meta-analysis, and permit survival rates to vary by sex, age and country in any manner in order to best fit estimates of all-cause mortality. Precedence is therefore given to their estimates of deaths, which, in most of these countries, are modelled based on indirect data sources, and therefore, potentially subject to errors. This could lead to unsubstantiated differences in survival rates across age, sex and country. This survival schedule selection procedure may also have contributed to the estimate by the Murray *et al.* that during the 1990s HIV prevalence was higher among men than in women. This has not been found in data from cohort studies from that time [6–13] (Fig. 1), although the comparison between estimates and data is somewhat complicated by the different age groups for which results are available.

There are greater proportionate differences between the Murray *et al.* and UNAIDS estimates for other countries outside Africa. Across North America, Europe, Central Asia and Australasia, the total discrepancy in PLHIV is

Box 1. Summary of Joint United Nations Programme on HIV/AIDS estimation method

Joint United Nations Programme on HIV/AIDS (UNAIDS) provides guidance, support and tools for countries to produce their own estimates of HIV and other indicators which are compiled into a set of global statistics. These tools are continuously developed and updated in collaboration with a reference group of epidemiologists, demographers and statisticians (www.epidem.org). Countries determine whether to produce estimates for a whole country at once or to build this up from estimates for regions and/or for multiple sub-populations. For each modelled country or region of a country, a decision is made about whether the epidemic is 'generalised' (the epidemic has spread widely throughout the general population) or 'concentrated' (the epidemic has remained largely confined to key populations, such as sex workers and MSM).

For generalised epidemics, there are typically two main data sources: prevalence estimates among women attending antenatal care (ANC) and prevalence estimates from nationally representative household based surveys. If a country does not have a population-based survey, it is then assumed that a bias exists in the prevalence measured in the ANC vs. the true level in the general population, the value for which is informed by a systematic analysis of countries that do have both types of prevalence data [38].

A model is fit to these data in a Bayesian framework that propagates uncertainty in the prevalence measurements [39–41], making assumptions about the survival time with HIV based on a direct analysis of cohort data [4] and incorporating programmatic information on the number of people on ART. A sample of epidemic curves are so produced for each population and these are randomly combined with epidemic curves from other populations to produce a set of estimated epidemic curves for the whole country. Consistency with all-cause mortality [42] is guaranteed by adjusting, where necessary, the non-HIV-related death rate. The total incidence rate for the whole population is disaggregated by age and sex, according to empirically derived distributions [20]. Results for numbers of new HIV infections, people living with HIV (PLHIV) and AIDS death are generated with estimated measures of uncertainty that reflect the sampling errors in the prevalence data as well as assumed variances imposed on multiple parameters. Those variances are not currently empirically derived and arguably have been too tightly constrained.

In settings with concentrated epidemics wherein there exists a well functioning system by which new HIV diagnoses are reported and counted, countries will normally follow their own procedures for estimating new infections, PLHIV and AIDS death. In computing global total, UNAIDS produces sets of estimates that correspond closely to these but these may not be published separately.

In other settings with concentrated epidemics, data on HIV prevalence among defined key groups and estimates of the sizes of these populations are assembled and the model is fit to these. The population size data will most often be derived empirically [30], or based on regional values [43–46], but a consensus among local experts drawing on ancillary information sources can be used if other data are not available. Additional epidemiological and behavioural data on these populations may be used to specify a rate of population turnover or additional rate of mortality. Further adjustment can be made to ensure a match in sex ratio of reported AIDS death in a vital registration system or if additional data from surveys of ANC records indicate this is necessary.

In all settings, the impact of interventions are specified by fitting the model to program data on the numbers on ART and women receiving prevention of mother-to-child transmission services. Assumptions are made on the impact of ART [47] and prevention of mother-to-child transmission [48] based on the direct estimation of relevant parameters with large, high-quality, geographically varied longitudinal data.

The models, data and actual files used for estimation are all available for free download from <http://apps.unaids.org/spectrum/>. The methods in all the estimation process are fully described in a series of open-access publications that are indexed at <http://www.epidem.org/publications>. Further information on the process by which the UNAIDS methods are developed is available at www.epidem.org.

1.7 million (UNAIDS PLHIV estimate 3.4 million vs. Murray *et al.*, 1.7 million). This too accounts for almost one third on the total global difference in the estimates. In these regions, the epidemics are concentrated among those at greatest risk of infection and Murray *et al.* assert that these

'concentrated epidemics have been systematically over-estimated by a factor on average of more than two'. Fortunately, however, many of these countries have strong case-based surveillance data that can be used to investigate these differences.

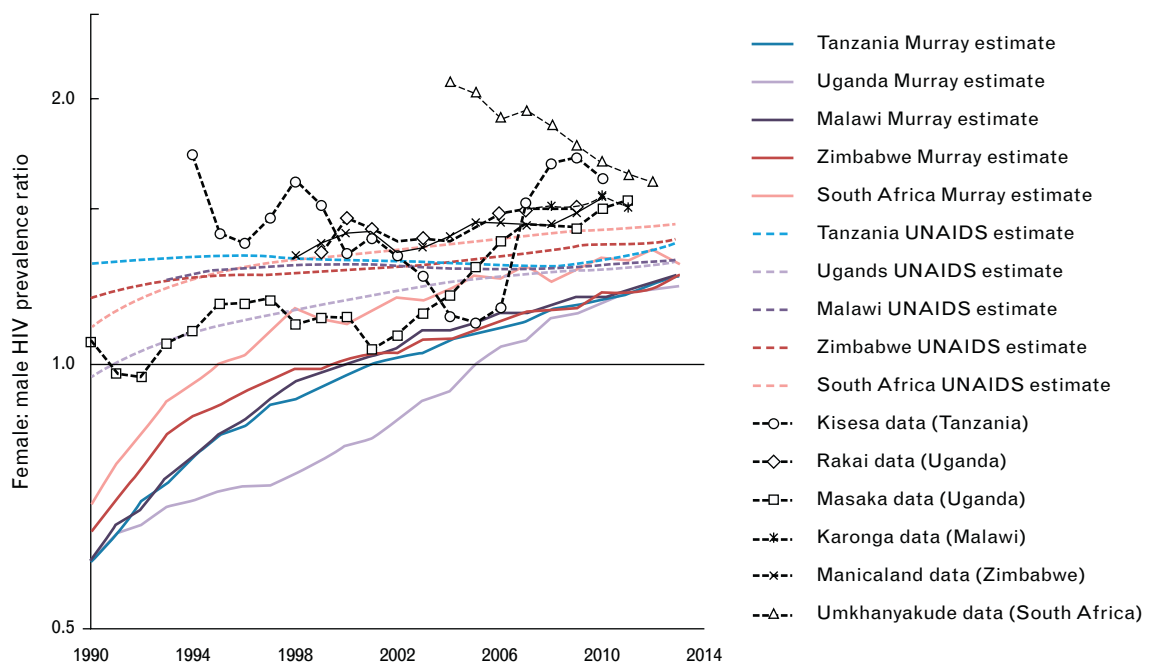


Fig. 1. Female-to-male prevalence ratios in the Murray *et al.* estimates [ratio of numbers of women-to-men people living with HIV (PLHIV), all ages] (solid coloured lines), in UNAIDS estimates (ratio of numbers of women to men PLHIV, all ages) (dashed colour lines) and measurements in available population level survey data among 15–49-year olds (markers with grey connecting lines). Note that the estimates based on data rely on an interpolation to provide a continuous time-series.

Numbers of new diagnoses can be considered as a rough, time-lagged proxy for HIV incidence. Broadly, number of new diagnoses are expected to underestimate new infections (as not all infected persons will seek HIV testing), but the number of cases could overstate new infections if there is double counting of patients (caused by, for instance, their presentation at multiple sites) or if many of the new cases were actually acquired abroad (for instance, among migrants from higher prevalence countries). In practice, in most places, measures are taken in order to avoid double counting [16].

In Table 1, countries in Europe and North America are ranked by the number of newly diagnosed HIV infections they report. In general, Murray *et al.* estimates are substantially less than the numbers of new cases reported in a country, whereas UNAIDS estimates tend to be greater. These differences are consistent over time (Fig. 2a–d).

Some differences are quite extreme. For example, in the UK, the Murray *et al.* estimate for the number of new HIV infections among men (350 in 2010) is almost seven-fold less than the estimate from the United Kingdom Health Protection Agency for just MSM in England and Wales (~2300) [17].

Differences are also found in other countries with robust surveillance systems, such as Australia and Japan (Fig. 2e and f).

These comparisons do not support the contention of Murray *et al.* that their lower estimates of new infections or PLHIV are more likely to be correct in these regions, and perhaps others where additional data to cross-check the estimates are not available. The UNAIDS estimate are potentially consistent with not all newly infected persons being diagnosed, but it is not possible to confirm the accuracy of the estimates with these data.

The remainder of the global differences in the two estimates of PLHIV comes largely from Asia Pacific (1.7 million discrepancy) and Latin America (630 000 discrepancy). In these settings, epidemics are also concentrated and although there are less well developed systems for reporting cases, many countries are assumed to have good vital registration systems. In the regions where vital registration systems are good (upon which Murray *et al.* estimates are based) and estimates of prevalence and size of risk groups (upon which UNAIDS estimate are based) are thought to be less reliable, we agree that estimates should rely more on mortality data in addition to the epidemiological data. UNAIDS is already doing this for Argentina, Mexico and Brazil in the latest round of estimates [20]. Overall, the discrepancy in the 2013 numbers of new infections, PLHIV and deaths, in those countries in Latin America and Asia with concentrated epidemics but good vital registration systems, amounts to 60 000 fewer new infections, 1.1 million fewer PLHIV and 55 000 fewer AIDS deaths in the Murray *et al.* estimates compared with UNAIDS,

Table 1. Countries with good case-based reporting systems in Europe, United States of America, Canada and Russian Federation in 2012 (except USA, for which data are for 2011).

Country	Rank in number of newly diagnosed HIV infections	Reported newly diagnosed HIV infections	Murray <i>et al.</i> estimated new infections	Relative difference between Murray <i>et al.</i> new infection estimate and reported newly diagnosed HIV cases (%)	UNAIDS estimate	Relative difference between UNAIDS estimate and reported newly diagnosed HIV cases (%)
Russian Federation	1	75 708	36 600	-52		
United States of America	2	49 273	26 200	-47		
Ukraine	3	16 872	13 100	-22	8604	-49
United Kingdom	4	6358	470	-93	6755	6
France	5	4066	2430	-40	6856	69
Italy	6	3898	3050	-22		
Spain	7	3210	2210	-31	3262	2
Germany	8	2953	1710	-42		
Canada	9	2062	850	-59	3122	51
Kazakhstan	10	2014	2700	34		
Belgium	11	1227	213	-83		
Belarus	12	1223	720	-41	2728	123
Poland	13	1085	470	-57		
Turkey	14	1068	590	-45		
Greece	15	1059	52	-95		
Netherlands	16	976	280	-71		
Tajikistan	17	814	790	-3	1668	105
Republic of Moldova	18	757	560	-26	1392	84
Portugal	19	721	2390	231		
Kyrgyzstan	20	700	820	17	870	24
Switzerland	21	643	350	-46	698	9
Georgia	22	526	67	-87	639	21
Azerbaijan	23	517	403	-22	1163	125
Romania	24	489	300	-39	608	24
Israel	25	487	109	-78		
Sweden	26	363	60	-83		
Ireland	27	339	57	-83		
Latvia	28	339	260	-23		
Estonia	29	315	98	-69		
Austria	30	306	540	76		

Countries are ranked by their reported number of newly diagnosed HIV infections (top 30), a proxy for new HIV infections. Some Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates, denoted by '...', are not published by UNAIDS but UNAIDS' files are configured to match incidence to numbers of reported cases. Relative differences are computed as 'Estimate - Reported New Cases/Reported New Cases'. Source [1,14,15,18]. UNAIDS, Joint United Nations Programme on HIV/AIDS.

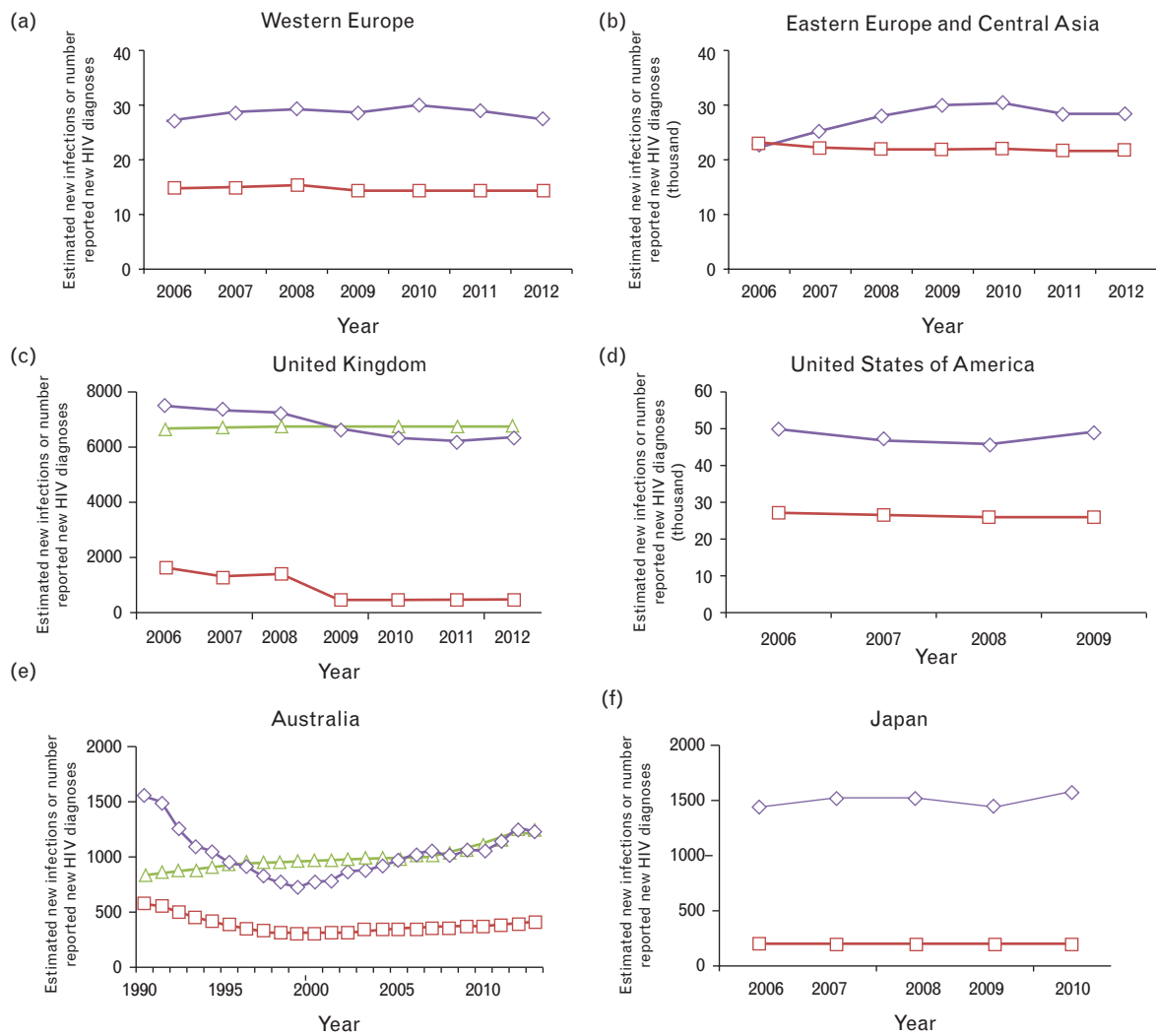


Fig. 2. Comparison between Murray *et al.* and Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates of new infections with case-report data in (a) Western Europe, (b) Eastern Europe and Central Asia, (c) United Kingdom, (d) United States of America, (e) Australia and (f) Japan. Red line with squares is the estimate of new HIV infections from Murray *et al.*; green line with triangles is UNAIDS estimate of new infections; purple line with diamonds is the country-reported number of new HIV diagnoses. UNAIDS estimates are not published for Japan, the United States of America or some European countries. Source: [1,14,16,18,19].

equivalent to about 3% of the overall UNAIDS estimates for each indicator.

Nevertheless, other data – where they exist – in those countries with good vital registration systems that have not been incorporated into the Murray *et al.*, estimates can provide a useful check on derived estimates. For instance, there have been two HIV prevalence surveys in Dominican Republic, in 2002 and 2007 (samples sizes 26 217 and 55 170, respectively). Multiplying prevalence estimates from those (1 and 0.8%, respectively [21]) by corresponding population sizes estimates [22] gives estimates of PLHIV aged 15–49 years of 46 000 and 40 000, respectively. Comparatively, Murray *et al.* estimates for PLHIV of all ages, at 17 500 and 19 600,

respectively, are less than half these values. In contrast, the UNAIDS estimates for PLHIV of all ages, at 70 000 and 55 000, are greater which may be partly explained by children and adults over 50 years living with HIV. In Brazil, Murray *et al.* estimate 396 000 (263 000–515 000) PLHIV, compared with the UNAIDS estimate of 726 000 (664 000–808 000); but the Brazilian government reports [23] a total of 436 000 PLHIV either in pre-ART care or on ART – more than the point estimate in Murray *et al.*

Arguably, these findings do not support the contention of Murray *et al.*, that their estimates are more likely to be correct than any other estimates, even in these settings where appropriate prevalence data are relatively sparse.

Difference in view of mortality trends over time

UNAIDS and Murray *et al.* estimates show that ART has driven large declines in mortality, the most dramatic being in southern and eastern Africa. However, the Murray *et al.* estimates indicate a somewhat more modest reduction in deaths than do those from UNAIDS.

Again, there are direct empirical data from population cohorts in several settings in Africa that can be used to assess the impact of ART (Fig. 3a–c). These data were not incorporated into either the Murray *et al.* or the UNAIDS estimates. These cohort data do indeed exhibit strong reductions in the rate of AIDS deaths – falls on the order of 50% reductions in mortality among PLHIV – consistent in magnitude with the decline reported by UNAIDS. It maybe the case, however, that the intensively researched populations have benefitted by a greater provision of ART than is available in the rest of their countries, and so could have experienced larger mortality reductions than at the national level.

Conclusion

It is useful and welcome that two different methods have been applied to estimate the same quantities. Most striking is the overall similarity in the estimates, rather than the differences – both show approximately 30 million people worldwide living with HIV and that enormous gains in life years have been generated by ART. It is inevitable that differences in the methods, related though they are, will lead to some differences in the results. We see this as an opportunity to investigate and learn from how different approaches and assumptions can affect results. Although we do not believe either set of estimates will be uniformly correct, our further investigations with additional empirical data do not lend support to the central contention of Murray *et al.* that their estimates should necessarily be preferred over others. Rather, we find no evidence that either set of estimates can be considered more accurate than the other, and indeed both will – in places – exhibit discrepancies with other data.

It is a significant and highly valuable contribution of Murray *et al.*, in that study and in their previous work [25], to have produced estimates of breakdowns by mortality cause. We agree that leveraging mortality data can strengthen estimates of HIV, and other diseases, where those data are available. However, we also believe that estimation methods should appropriately balance this with information from other epidemiological data sources, including prevalence data, case-based surveillance and program data. Without doing so, as we have described, estimates can be generated that are clearly at odds with robust data available in the countries, and such contradictions will not assist planners in their evaluation

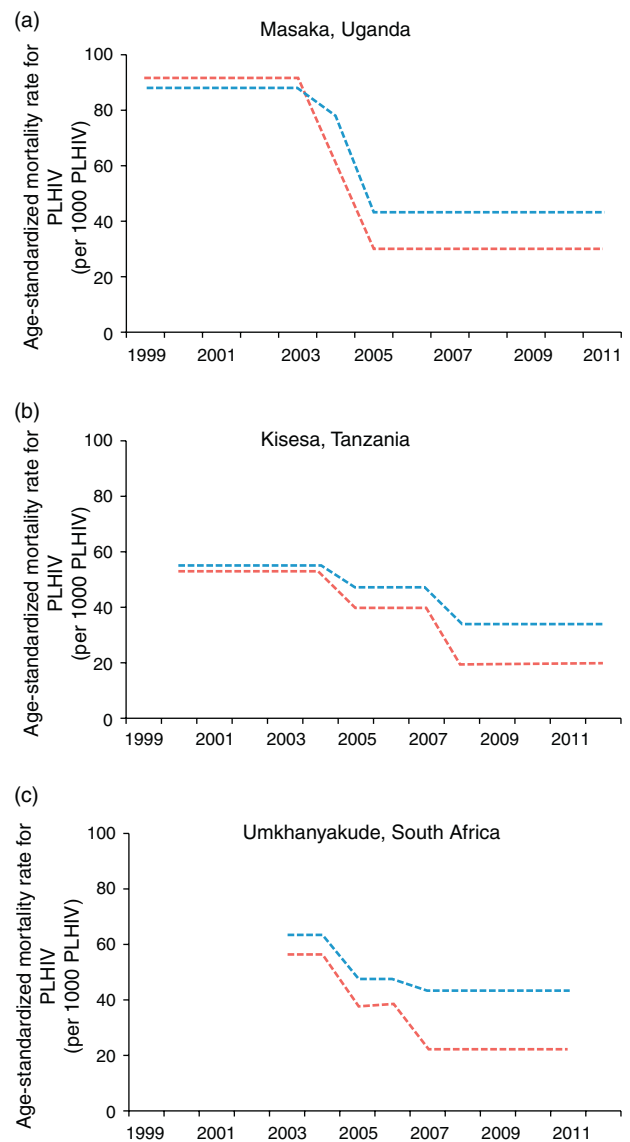


Fig. 3. Empirical measures of death rates among people living with HIV from cohort studies in (a) Uganda, (b) Tanzania and (c) South Africa. Rates of men are in blue and rates in women are in red. These are the reported age-standardized mortality rates among HIV-infected individuals for three periods: pre-ART, ART scale-up, and post-ART scale-up, plotted as uniform over the calendar time to which those definitions correspond [24]. ART, antiretroviral therapy.

of their interventions or in setting priorities. Future work, for all those generating estimates in HIV, should seek a fuller integration of these disparate data sources. For its part, UNAIDS is seeking to include data from tests for recent infection [26], case reports, vital registration [27], programmes for prevention of mother-to-child transmission and more details on ART programmes in future estimates (audits of ART numbers, viral load measurements in population-based surveys and country-level data on survival and retention on ART), while also

continuing to confront estimates with empirical data to check the validity of its methods [28,29].

All methods for producing estimates have their limitations. In this review, we have not attempted to be systematic in comparing the two sets of estimates, but have rather sought to identify and examine the largest and most important differences. There will be examples in both sets of estimates which seem to be falsified by other data – which is a sign that neither set can be considered perfect. This also underlines the difficulty in generating estimates. The reliance, for instance, of the UNAIDS method on the reported numbers on ART and its assumptions of a uniform impact of ART on transmission and mortality risk may make it vulnerable to over-estimating the impact of ART, where programs are not able to deliver the same standard of care as has been reported in studies or if there are any errors in reports of numbers on ART. The reliance, exclusively until recently, on the consistency in prevalence data in concentrated epidemics, over time and of the veracity of empirically derived, but nevertheless uncertain, estimates of sizes of key populations [30] could also lead to biased results. Nevertheless, the UNAIDS numbers and trends in new infections and deaths seem directionally consistent with other independent empirical data from cohort studies, for example especially in the large generalised epidemics. Meanwhile, the Murray *et al.* method suffers, by necessity, on a reliance on uncertain models for mortality in most of the settings with largest epidemics, and elsewhere is subject to questions about the extent to which verbal autopsy data can be relied upon [31,32] and the difficulties of adjusting for misclassification of death caused by AIDS.

There is increasingly a focus on country leaders taking ownership of HIV programmes, and other public health programmes, and there have been many calls for the greater use of data in decision making. It is therefore extremely helpful if the generation and use of data for public decision making are led by countries. In a recent editorial, Atun [33] calls for transparency and sharing of the methods and data used to make estimates and an emerging theme in programme planning and evaluating is understanding process at a finer spatial scale [34]. In this context, the UNAIDS approach of empowering countries to construct their own estimates, increasingly at sub-national level [35,36], with guidance on appropriate methods and assumptions, with most datasets and models freely accessible and continuously subject to peer review, seems well placed. On the other hand, there are advantages to synthesising data from multiple countries together in order to produce an internally consistent view of global health across disease and countries. These different approaches are complementary and the value that they each provide to country programme planners can be enhanced through coordination and data sharing.

We may stand at the edge of a revolution in data sharing in global health, as The United States President's Emergency Plan for AIDS Relief, The Global Fund for AIDS, Tuberculosis and Malaria and other agencies open up their records, and countries and international agencies increase their efforts to distribute epidemiological data [37]. This is an exciting time, and estimates and evaluations will be strengthened through an iterative scientific investigative process that should result in meaningful gains in reliable information for country programme planners.

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Conflicts of interest

There are no conflicts of interest.

Authors are members of the UNAIDS Reference Group on Estimates, Modelling, Projections.

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